Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease.

Bibliographic Source(s)

Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017 Sep;153(3):827-34. [33 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
NO	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
NO	Multidisciplinary Group

YES	Methodologist Involvement
▮▮▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▮▯	External Review
▮▮▮▮▮	Updating

Recommendations

Major Recommendations

Definitions for the quality of evidence (High, Moderate, Low, Very low) and strength of recommendation (Strong, Conditional, No recommendation) are provided at the end of the "Major Recommendations" field.

In adults with active inflammatory bowel disease (IBD) treated with anti-tumor necrosis factor (TNF) agents, the American Gastroenterological Association (AGA) suggests reactive therapeutic drug monitoring to guide treatment changes. (Conditional recommendation, Very low quality of evidence)

Comment: Table 4 in the original guideline document summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.

In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring. (No recommendation, Knowledge gap)

In adult patients with IBD being started on thiopurines, the AGA suggests routine thiopurine methyltransferase (TPMT) testing (enzymatic activity or genotype) to guide thiopurine dosing. (Conditional recommendation, Low quality of evidence)

Comment: Routine laboratory monitoring, including complete blood count (CBC), should be performed, regardless of TPMT testing results.

In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes. (Conditional recommendation, Very low quality of evidence)

Comment: When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, the AGA suggests a target 6-thioguanine (6-TGN) cutoff between 230 and 450 pmol/8 x 10^8 red blood cells (RBCs) when used as monotherapy; optimal 6-TGN cutoff when thiopurines are used in combination with anti-TNF agents is uncertain.

In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring. (Conditional recommendation, Very low quality of evidence)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Definitions on Strength of Recommendation

	Wording in Guideline	For the Patient	For the Clinician
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"No recommendation"		The confidence in the effect estimate is so low that any recommendation is speculative at this time.

Clinical Algorithm(s)

An algorithm titled "Therapeutic Drug Monitoring in Inflammatory Bowel Disease: Clinical Decision Support Tool" is provided on the Gastroenterology Journal Web site .

Scope

Disease/Condition(s)

Inflammatory bowel disease

Guideline Category

Management

Treatment

Clinical Specialty

Gastroenterology

Internal Medicine

Intended Users

Physicians

Guideline Objective(s)

- To present the official recommendations of the American Gastroenterological Association (AGA) on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD)
- To inform appropriate utilization of TDM with anti-tumor necrosis factor (TNF)-α agents and thiopurines
- To determine the role of testing the genetic or enzymatic activity of thiopurine methyltransferase (TPMT) before starting a thiopurine

Target Population

Patients with inflammatory bowel disease treated with anti-tumor neurosis factor medications or thiopurine medications

Note:

> This guideline does not address the role of TDM in patients treated with vedolizumab or ustekinumab.
> Non-anti-tumor necrosis factor (TNF) biologics are not discussed in these guidelines.

Interventions and Practices Considered

1. Reactive therapeutic drug monitoring (TDM)
2. Routine thiopurine methyltransferase (TPMT) testing (enzymatic activity or genotype)
3. Reactive thiopurine metabolite monitoring

Note: The following were considered but not recommended or no recommendation was made: routine proactive TDM, routine thiopurine metabolite monitoring.

Major Outcomes Considered

- Clinical remission
- Mucosal healing (endoscopic remission)
- Serious adverse events

- Cost
- Drug or metabolite concentration
- Patient convenience
- Clinical disease activity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Formulation of Clinical Questions

Using the PICO format, which frames a clinical question by defining a specific population (P), intervention (I), comparator (C), and outcomes (O), the team finalized 5 questions (refer to Table 1 in the technical review [see the "Availability of Companion Documents" field]). The first set of PICOs focused on therapeutic drug monitoring (TDM) for anti-anti-tumor necrosis factor (TNF) agents, and the second set of PICOs on TDM for thiopurines. Questions focused on comparing different strategies of TDM classified as reactive TDM or routine proactive TDM. *Reactive TDM* is defined as TDM performed in response to active inflammatory bowel disease (IBD) (ongoing active inflammation based on biochemical, endoscopic, or radiologic assessment, usually with symptoms) after a period of quiescent disease, or continued inflammation without achieving remission with index therapy; of note, a small fraction of patients, especially those with active Crohn's disease (CD) (active inflammation) may be asymptomatic, and the concept of reactive TDM also applies to those patients. *Routine proactive TDM* was defined as TDM performed in patients regardless of clinical status (generally in quiescent disease) periodically as part of routine clinical care. The comparator strategy relied on empiric treatment changes—for anti-TNF agents, this focused on a stepwise approach of empiric escalation of therapy or switching to different treatment agents within or outside the index class (i.e., with same putative mechanism of action or with a different mechanism of action). Potentially relevant patient-important outcomes were considered and rated in terms of importance through consensus; clinical remission was considered critical for decision making, whereas mucosal healing (endoscopic remission), serious adverse events, cost, drug or metabolite concentration, and patient convenience were considered important outcomes. The technical report panel recognized limitations of using a clinical disease activity as an outcome measure, especially for CD, but still believed that in the current context, it is the most consistently reported outcome in clinical practice and is important for patients.

Search Strategy and Study Selection Criteria

The literature search was performed on March 6, 2016, and details of the search strategy are reported in the technical report supplementary material (see the "Availability of Companion Documents" field). Studies were selected for inclusion based on PICO theme. Due to lack of high-quality randomized controlled trials (RCTs) informing each question, the study selection and data synthesis approach were customized for each question. For PICO #1 (reactive TDM) and PICO #2 (routine proactive TDM), for anti-TNF agents, the technical report panel included RCTs, comparative observational studies, or cohort studies in adults with IBD, with either active IBD or quiescent disease, treated with anti-TNF agents, who underwent TDM (i.e., measurement of drug levels and/or anti-drug antibodies [ADAbs]). Due to the paucity of high-quality RCTs and observational comparative studies for PICOs #1 and #2, the panel relied on cohort studies that reported differences in outcomes of patients depending on trough level and/or

presence of ADAb, in response to empiric dose escalation and/or switching therapies. This provided indirect evidence on potential risks and benefits of TDM-guided treatment decisions compared with empiric treatment changes. For PICO #3 on the role of thiopurine methyltransferase (TPMT) enzyme activity or genotype before starting thiopurines, the panel included RCTs in patients with IBD who were started on thiopurines, based on either TPMT guidance or empirically, and evaluated safety and efficacy of therapy. For PICOs #4 and #5 on application of TDM strategies for thiopurines, a similar approach was adopted, wherein, if high-quality RCTs or observational comparative studies were lacking, cohort studies were used to inform evidence indirectly.

To inform optimal target trough concentrations and their performance, the panel initially searched for RCTs or observational comparative studies that report differences in patient outcomes based on different target trough concentration thresholds. In the absence of comparative studies, they chose cohort and cross-sectional studies that reported correlation between different thresholds and presence or absence of clinical remission (or response) and assessed the pooled proportion of patients "not in remission" above certain predefined thresholds. Of note, these were not framed as PICOs, but are rather presented semi-quantitatively to inform clinical guidelines.

To inform evidence pertaining to these focused questions, a systematic literature search of multiple electronic databases on TDM in IBDs was conducted by an experienced medical librarian using a combination of controlled vocabulary supplemented with keywords, with input from the technical review authors. The search was conducted from inception to March 6, 2016, and the databases included: Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE and Ovid Cochrane Database of Systematic Reviews (detailed search strategy listed in the supplementary materials). Technical review context experts and methodologist independently reviewed the title and abstract of studies identified in the search to exclude studies that did not address the focused question based on prespecified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information, and relevant articles at end of this process were selected for each question. Conflicts in study selection at this stage were resolved by consensus, referring back to the original article in consultation with clinical content experts. This search was supplemented with a recursive search of the bibliographies of recently published systematic reviews on this topic, to identify any additional studies. The panel also reviewed conference proceedings from major gastroenterology conferences from 2011 through 2016, and contacted experts in the field for any potential unpublished studies. They restricted their search to English language and human studies. Filters were applied to exclude editorials, letters to the editor and case reports.

Number of Source Documents

The search identified 3,715 unique articles. The technical review panel reviewed full texts of 263 studies. The following were included in quantitative synthesis:

Population, intervention, comparator and outcome (PICO) #1 = 4 studies
PICO#2 = 1 study
Infliximab level = 6 studies, adalimumab level = 6 studies, certolizumab levels = 1 pooled analysis of 9 trials
PICO#3 = 3 studies
PICO#4 = 1 study
PICO#5 = 2 studies
Thiopurine metabolite levels = Meta-analysis of 17 studies

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence

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Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Statistical Analysis

When comparative studies were available, pooled relative risk (RR) and 95% confidence intervals (CI) were calculated using DerSimonian-Liard random-effects model. For population, intervention, comparator and outcomes (PICOs) #1 and #4, as well as in assessing performance of different trough concentration thresholds, the panel estimated weighted pooled proportion of patients in different relevant categories, using random-effects meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic, and values >50% were considered suggestive of significant heterogeneity. Small study effects were examined using funnel plot symmetry and Egger's regression test, though it is important to recognize that these tests are unreliable when the number of studies is <10. Statistical analyses were performed using RevMan, version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) or Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ).

Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (or confidence in summary effect estimates). In this approach, direct evidence from randomized controlled trials (RCTs) starts at high quality and can be rated down based on risk of bias in the body of evidence (or study quality), indirectness (addressing a different but related population, intervention, or outcome, from the one of interest), imprecision (of summary estimate and boundaries of 95% CI), inconsistency (or heterogeneity), and/or publication bias to levels of moderate, low, and very low quality. Due to inherent limitations in observational studies (i.e., selection bias, unmeasured confounding), evidence derived from observational studies starts at low quality, and is then potentially downgraded based on the factors mentioned, or can be upgraded in case of dose-response relationship and large magnitude of effect.

Evidence-to-Decision Framework

Because the technical review was used to inform the development of clinical guidelines, besides a comprehensive risk–benefit analysis and the accompanying quality of evidence, information about additional factors, such as patients' values and preferences, cost-effectiveness, and resource utilization

were also considered.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Gastroenterological Association (AGA) process for developing clinical practice guidelines follows the standards set by the Institute of Medicine. This process is described in more detail elsewhere and was used in developing the technical review (see the "Availability of Companion Documents" field) and the guideline. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework was used to evaluate the certainty of the evidence and grade the strength of the recommendations. Understanding of this guideline and the evidence supporting the recommendations will be enhanced by reading the Technical Review. The guideline panel and the authors of the technical review met face-to-face on February 26, 2017 to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although quality of evidence (see the "Rating Scheme for the Strength of the Evidence" field) was a key factor in determining the strength of the recommendation (see the "Rating Scheme for the Strength of the Recommendations" field), the panel also assessed the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions on Strength of Recommendation

	Wording in Guideline	For the Patient	For the Clinician
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"No recommendation"		The confidence in the effect estimate is so low that any recommendation is speculative at this time.

Cost Analysis

While cost is usually factored into the recommendation, in this situation it was not feasible to accurately assess cost-effectiveness, given the variable costs of the commercial trough concentration and antibody testing assays throughout the United States and internationally. See the technical review (see the "Availability of Companion Documents" field) for more information.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The original guideline document presents the official recommendations of the American Gastroenterological Association (AGA) on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD). The guideline was developed by the AGA's Clinical Guidelines Committee and approved by the AGA Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Therapeutic drug monitoring (TDM) may be helpful to guide appropriate treatment changes.
- A systematic and algorithmic assessment of drug concentration (and anti-drug antibody [ADAb]) can help objectively evaluate potential reasons for failure of therapy and define next steps in management, and proactively provide opportunities for optimizing therapy to maximize chances of treatment success.

See the technical review (see the "Availability of Companion Documents" field) for additional information about potential benefits.

Potential Harms

- Besides the mild inconvenience of blood test for therapeutic drug monitoring (TDM), there is potential misclassification and missed treatment optimization opportunities due to suboptimally defined thresholds for both drug concentration and ant-drug antibodies (ADAb).
- TDM is performed through a blood test generally just before next due dose, which can cause a small inconvenience. However, there are additional potential harms of downstream interventions from TDM testing because thresholds for therapeutic trough concentration and ADAbs are not very well-defined. Therapeutic trough is dynamic, depending on phase of intervention (induction vs maintenance therapy), treatment target (clinical remission vs endoscopic remission), and phase of disease activity (severe active vs mild active disease; luminal disease vs perianal disease). Likewise, threshold ADAb levels that define immunogenicity and predict low likelihood of response to dose escalation are not well-defined and are variable across assays. Therefore, due to variable thresholds, which have suboptimal discriminatory performance, strict adherence to TDM-guided treatment changes can potentially result in inappropriate treatment changes in some patients who might have responded to empiric escalation of therapy.
- Incidental findings during thiopurine metabolite testing can potentially result in unwarranted

treatment changes. With the availability of several newer and more effective therapeutic agents over the last decade, attempts at close metabolite monitoring and serial dose adjustments can potentially delay more effective therapy in a subset of underdosed patients who may be inherently thiopurine-resistant.
- While testing for thiopurine methyltransferase (TPMT) may potentially delay starting therapy for approximately 1 to 2 weeks (while awaiting test results), it is likely inconsequential given the slow onset of action of this medication.

See the "Potential harms of intervention" sections in the technical review (see the "Availability of Companion Documents" field) for additional information about potential harms.

Qualifying Statements

Qualifying Statements

Understanding of this guideline and the evidence supporting the recommendations will be enhanced by reading the Technical Review (see the "Availability of Companion Documents" field).

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017 Sep;153(3):827-34. [33 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Sep

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Guidelines Committee

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Financial Disclosures/Conflicts of Interest

The authors disclose no conflicts.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site .

Availability of Companion Documents

The following are available:

Casteele NV, Herfarth H, Katz J, Fack-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel disease. Gastroenterology. 2017;153:835-57. Available from the Gastroenterology Journal Web site .

Casteele NV, Herfarth H, Katz J, Fack-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel disease. Online supplement. 2017;153:857.e1-e6. Available from the Gastroenterology Journal Web site .

AGA guidelines policies & procedures: process for developing guidelines. Bethesda (MD): American Gastroenterological Association (AGA); 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site .

The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site .

In addition, a continuing medical education activity is available from the Gastroenterology Journal Web site .

Patient Resources

The following is available:

IBD 115: therapeutic drug monitoring in IBD. Patient guide. [internet]. Bethesda (MD): American Gastroenterological Association (AGA). Available from the American Gastroenterological Association (AGA) Web site .

NGC Status

This NGC summary was completed by ECRI Institute on January 3, 2018. The information was verified by the guideline developer on February 9, 2018.

This NEATS assessment was completed by ECRI Institute on November 29, 2017. The information was verified by the guideline developer on February 1, 2018.

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